

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
27 December 2002 (27.12.2002)

PCT

(10) International Publication Number  
WO 02/102377 A1

- (51) International Patent Classification<sup>7</sup>: A61K 31/429, 31/47, 31/435
- (21) International Application Number: PCT/US02/18944
- (22) International Filing Date: 14 June 2002 (14.06.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
60/298,768 15 June 2001 (15.06.2001) US
- (71) Applicant (for all designated States except US): 3M INNOVATIVE PROPERTIES COMPANY [US/US]; 3M Center, Post Office Box 33427, Saint Paul, MN 55133-3427 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): MITRA, Sumita, B. [US/US]; 1952 Nature View Lane, West St. Paul, MN 55118 (US). SHELBURNE, Charles, E. [US/US]; 8116 Yates Avenue North, Brooklyn Park, MN 55443 (US). TOMAI, Mark, A. [US/US]; 8067 Enclave Bay, Woodbury, MN 55125 (US).
- (74) Agents: HOWARD, MarySusan et al.; Office of Intellectual Property Counsel, Post Office Box 33427, Saint Paul, MN 55133-3427 (US).
- (84) Designated States (national): AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK (utility model), SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:  
— with international search report  
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/102377 A1

(54) Title: IMMUNE RESPONSE MODIFIERS FOR THE TREATMENT OF PERIODONTAL DISEASE

(57) Abstract: The disclosure provides methods for the treatment and prevention of periodontal disease. In preferred embodiments, the invention provides for local treatment of periodontal tissues with a pharmaceutical composition including an immune response modifier (IRM) selected from the group of immune response modifiers comprising imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, oxazoloquinoline amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines.

## IMMUNE RESPONSE MODIFIERS FOR THE TREATMENT OF PERIODONTAL DISEASE

5

Field of the Invention

The invention is directed to methods for the treatment or prevention of periodontal conditions. Specifically the invention includes the novel use of immune response modifier compounds to treat or prevent periodontal disease. Preferred immune response modifiers are selected from the group of immune response modifiers comprising imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 10 imidazonaphthyridine amines, oxazoloquinoline amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines.

Background of the Invention

Periodontal disease or periodontitis is an inflammatory disease that results in the 15 destruction of both the hard and soft tissues supporting the teeth and has recently been hypothesized as a risk factor for cardiovascular disease. Beck et al. "Dental Infections and atherosclerosis, "American Heart Journal, 13:S528-533 (1999). It is estimated that over 10 million people in the United States are currently being treated for the more serious forms of this disease, with approximately 8 billion dollars spent for treatment each year.

20 Clinically, periodontitis is an inflammation of the periodontium and results in inflammation of the gingiva and may result in resorption of alveolar bone and recession of the gingiva. Recession of the gingiva can lead to exposure of the periodontal ligament allowing microorganisms to invade and destroy the ligament.

Infection by a few essential species of bacteria is important in initiating the host 25 inflammatory response that is responsible for the tissue destruction and ultimate loss of

teeth. Zambon, J.J., "Periodontal Disease, Microbial Factors," Ann. Periodontol., 1:879-825 (1996). The major pathogens associated with the disease have been identified and include *Porphyromonas gingivalis*, *Bacteroides forsythus* and *Actinobacillus actinomycetemcomitans*. Although essential to the pathogenesis, bacteria alone are

5 insufficient to cause the disease. Host factors such as hereditary predisposition and environmental factors such as smoking are believed to equally effect disease occurrence and severity of outcome.

Forms of periodontitis include early onset periodontitis (EOP), chronic adult periodontitis (AP), and refractory periodontitis (RP). Localized juvenile periodontitis is a

10 form of EOP which occurs in otherwise seemingly healthy adolescents and is associated with infection by *A. actinomycetemcomitans*. "Chronic adult periodontitis" is commonly associated with the presence of *B. forsythus*, *P. gingivalis*, many gram-negative asaccharolytic rods, and oral spirochetes. It typically occurs in patients over 35 years of age. Clinically, it resembles acute necrotizing ulcerative gingivitis imposed on rapidly

15 progressive periodontitis. Patients may lose 9 to 12 mm of gingival attachment in as little as six months.

Current treatment for periodontal disease is almost exclusively mechanical and surgical in nature most frequently including scaling and root planing to remove calculus deposits. However, the mechanical treatments do not affect the underlying cause of

20 disease. Antibiotics have also been used as an adjunct therapy, Loesche et al, "Treatment paradigms in periodontal disease", Compend. Contin. Educ Dental, 18(3):221-6, 228-30 (1997). Unfortunately, results have been disappointing because the antibiotic may not eliminate the bacteria responsible for the inflammatory component, and patients are subject to re-infection.

Accordingly, there is a continuing need for new and effective treatment and preventive measures for periodontal disease. The present invention is directed to this need.

### Summary of the Invention

5           The present invention provides methods for treating or preventing a periodontal condition comprising administering a therapeutically effective amount of an immune response modifier (IRM) compound directly to periodontal tissue in a patient affected by the periodontal condition. In preferred embodiments the IRM compound is selected from the group comprising imidazoquinoline amines, imidazopyridine amines, 6,7-fused  
10       cycloalkylimidazopyridine amines, imidazonaphthyridine amines, oxazoloquinoline amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines.

### Brief Description of the Drawings

FIG. 1 is a diagram illustrating periodontal anatomy;

15       FIG. 2 is a graph showing the proportion of *Porphyromonas gingivalis* in the plaque of infected mice;

FIG. 3 is a graph showing bone loss in infected mice;

FIG. 4a is a graph of bleeding index, gingival index and probing depth of a dog pre-treatment; and

20       FIG. 4b is a graph of bleeding index, gingival index and probing depth of a dog at two weeks post-treatment.

### Detailed Description

The present disclosure provides methods for treatment or prevention of an oral condition, such as periodontal disease, using an immune response modifier (IRM) compound. As used herein, "immune response modifier compound", means a compound which induces the production of one or more cytokines, e.g., Interferon ( $\alpha$ ), Tumor Necrosis Factor, and Interleukin-12, from hematopoietic cells including dendritic cells and/or monocyte/macrophages. Examples of such compounds include the CpG oligonucleotides, lipopolysaccharides, polyinosinic:polycytidylic acid complexes, and polypeptides and proteins known to induce cytokine production from dendritic cells and/or monocyte/macrophages.

In preferred embodiments, the IRM compound is selected from the group comprising imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, oxazoloquinoline amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines. Methods for preparing such IRMs and pharmaceutical compositions containing them are disclosed in, for example, U.S. Patent Nos. 4,689,338; 5,389,640; 5,268,376; 4,929,624; 5,266,575; 5,352,784; 5,494,916; 5,482,936; 5,346,905; 5,395,937; 5,238,944; 5,525,612; 5,175,296; 5,693,811; 5,741,908; 5,939,090; 6,110,929; 4,988,815; 5,376,076; 6,194,425; 6,245,776; and 6,331,539; and PCT Publications WO 00/76505 and WO 00/76518. The entire disclosure of each of these patents and patent applications is incorporated herein by reference.

As used herein, "periodontitis" is an inflammation or degeneration, or both, of the dental periodontium, alveolar bone, cementum, and adjacent gingival tissue. Referring to FIG. 1, by way of review, each tooth consists of three parts, a crown 1, neck 2 and root 3.

The crown 1 is the part of the tooth that projects above the gingiva 4 and occludes with one or more other teeth in the opposite jaw. The neck 2 is the part of the tooth between the crown 1 and the root 3. The cemento-enamel junction (CEJ) 5 is the location where the cementum 6 of the root 3 and enamel 7 of the crown 1 meet. The root 3 is fixed in the tooth socket 8, or "alveolus". Most of the tooth is composed of dentin 10 that is covered by enamel 7 over the crown 1 and cementum 6 over the root 3. The cementum 6 over the root 3 is attached to the alveolar bone 11 by periodontal ligament 13 to form a fibrous joint between the tooth and its alveolus 8.

Thus, as used herein, "periodontal tissues" are the tissues surrounding and supporting a tooth and include the periodontal ligament, alveolar bone and gingiva. A "periodontal pocket" is a pathologically induced space extending below the cemento-enamel junction (CEJ) and resulting from break down of the alveolar bone and/or periodontal ligament.

The inflammatory nature of periodontitis is not yet fully understood, although a general model has been advanced, Page et al., "Advances in the pathogenesis of periodontitis: summary of developments, clinical implications and future directions", Periodontology 2000, 14:216-248 (1997). One hypothesis is that the normal immune response against the initiating bacteria, which would prevent the bacteria from causing disease, has been altered and becomes not just ineffective but contributory to the disease process, Mathur et al., "Cell-mediated immune system regulation in periodontal disease," Critical Rev. Oral. Bio. Med., 8:76-89 (1997). According to this hypothesis, in patients with minimal or no periodontal disease, the immune response is skewed towards a TH1 immune response, which is generally involved with controlling viruses and tumors. In patients with progressive periodontal disease, the immune response pathway is skewed

towards a TH2 response, characterized by activation of B cells to secrete antibodies. It is believed that the antibody response is ineffective against the bacteria, is usually of short duration, and does not lead to immune "memory". In addition, cytokines that are secreted by TH2 cells can activate inappropriate host tissue remodeling enzymes that contribute to the destruction of the connective tissue that holds the teeth to the jaw, and enzymes that cause the resorption of the alveolar bone around the teeth.

Another report sets forth a model of periodontal disease based on the T-cell dichotomy characterized by a higher proportion of IL-4 producing cells in periodontitis tissues, and hypothesize a role for TH2 cells in progressive lesions of the disease, Seymour G. J. et al., "Cellular immunity and hypersensitivity as components of periodontal destruction," Oral Dis., 2(1):96-101 (1996) This report has been recently supported by work by Bartova et al., "TH1 and TH2 cytokine profile in patients with early onset periodontitis and their healthy siblings," Mediators Inflamm., 9(2):115-20 (2000).

A different hypothesis that has been advanced is that the TH1 response, which activates a number of typical cytokines, can result in bone resorption as a result of osteoclast activation. Assuma et al., "IL-1 and TNF antagonists inhibit the inflammatory response and bone loss in experimental periodontitis", J. of Immunology, 160:403-409 (1998).

In another report, a cumulative cytokine profile has been observed in periodontitis consistent with the predominance of TH1-type cells in pathological tissues and with TH2-type cells, when present, being up-regulated under appropriate stimulation. Takeichi et al., "Cytokine profiles of T-lymphocytes from gingival tissues with pathological pocketing," J. Dent. Res., 79(8):1548-55 (August 2000). Both CD4 and CD8+ lymphocytes were shown to express TH1- and TH2-type cytokine messages.

In sum, the foregoing reports emphasize the relative lack of agreement on the mechanisms responsible for periodontal disease pathogenesis, and the lack of consensus for any medicinal approach to disease management.

Many imidazoquinoline amine, imidazopyridine amine, 6,7-fused  
5 cycloalkylimidazopyridine amine, imidazonaphthyridine amines, oxazoloquinoline  
amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amine compounds  
have demonstrated potent immunomodulating, antiviral and antitumor (including  
anticancer) activity, and have also been shown to be useful as vaccine adjuvants to  
enhance protective immune system response to vaccines. Recently, it has been found that  
10 many of these IRM compounds can inhibit TH2 immune responses, as well as enhance  
TH1 immune responses. See eg. U.S. Patent 6,039,969, the entire disclosure of which is  
incorporated herein by reference.

Although the immunology of periodontal disease remains controversial the  
inventors have now discovered that treatment with immune response modifying  
15 compounds may benefit patients with periodontitis and treat the underlying infection.  
Specifically, treatment with IRM compounds can reduce the destruction of the alveolar  
bone or periodontal ligament. If treatment is administered at an appropriate time before  
destruction of periodontal tissues begins, the invention can also be used to modulate the  
patient's immune response to effectively prevent clinical signs of periodontal disease. Thus  
20 the IRM compositions can have both therapeutic and prophylactic value.

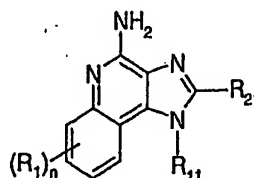
A "patient" includes humans and animals

A pharmaceutical composition useful in the method of the invention includes an  
immune response modifier (IRM) compound. Preferred compositions include compounds  
selected from the group of immune response modifiers comprising imidazoquinoline



amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, oxazoloquinoline amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines.

Preferred immune response modifier compounds include 1H-imidazo[4,5-c]quinolin-4-amines defined by one of Formulas I-V below:



I

wherein

$R_{11}$  is selected from the group consisting of alkyl of one to ten carbon atoms, hydroxyalkyl of one to six carbon atoms, acyloxyalkyl wherein the acyloxy moiety is alkanoyloxy of two to four carbon atoms or benzyloxy, and the alkyl moiety contains one to six carbon atoms, benzyl, (phenyl)ethyl and phenyl, said benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently selected from the group consisting of alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms and halogen, with the proviso that if said benzene ring is substituted by two of said moieties, then said moieties together contain no more than six carbon atoms;

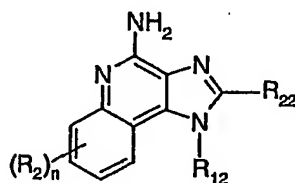
$R_{21}$  is selected from the group consisting of hydrogen, alkyl of one to eight carbon atoms, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently selected from the group consisting of alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms and halogen, with the proviso that when the benzene ring is substituted

by two of said moieties, then the moieties together contain no more than six carbon atoms;

and

each  $R_1$  is independently selected from the group consisting of alkoxy of one to four carbon atoms, halogen, and alkyl of one to four carbon atoms, and  $n$  is an integer

5 from 0 to 2, with the proviso that if  $n$  is 2, then said  $R_1$  groups together contain no more than six carbon atoms;



II

wherein

10  $R_{12}$  is selected from the group consisting of straight chain or branched chain alkenyl containing two to ten carbon atoms and substituted straight chain or branched chain alkenyl containing two to ten carbon atoms, wherein the substituent is selected from the group consisting of straight chain or branched chain alkyl containing one to four carbon atoms and cycloalkyl containing three to six carbon atoms; and cycloalkyl

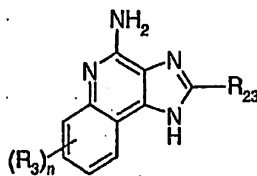
15 containing three to six carbon atoms substituted by straight chain or branched chain alkyl containing one to four carbon atoms; and

$R_{22}$  is selected from the group consisting of hydrogen, straight chain or branched chain alkyl containing one to eight carbon atoms, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene

20 ring by one or two moieties independently selected from the group consisting of straight chain or branched chain alkyl containing one to four carbon atoms, straight chain or branched chain alkoxy containing one to four carbon atoms, and halogen, with the proviso

that when the benzene ring is substituted by two such moieties, then the moieties together contain no more than six carbon atoms; and

each  $R_2$  is independently selected from the group consisting of straight chain or branched chain alkoxy containing one to four carbon atoms, halogen, and straight chain or branched chain alkyl containing one to four carbon atoms, and  $n$  is an integer from zero to 2, with the proviso that if  $n$  is 2, then said  $R_2$  groups together contain no more than six carbon atoms;



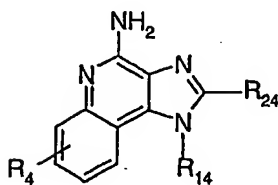
III

wherein

$R_{23}$  is selected from the group consisting of hydrogen, straight chain or branched chain alkyl of one to eight carbon atoms, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently selected from the group consisting of straight chain or branched chain alkyl of one to four carbon atoms, straight chain or branched chain alkoxy of one to four carbon atoms, and halogen, with the proviso that when the benzene ring is substituted by two such moieties, then the moieties together contain no more than six carbon atoms; and

each  $R_3$  is independently selected from the group consisting of straight chain or branched chain alkoxy of one to four carbon atoms, halogen, and straight chain or branched chain alkyl of one to four carbon atoms, and  $n$  is an integer from zero to 2, with

the proviso that if n is 2, then said R<sub>3</sub> groups together contain no more than six carbon atoms;



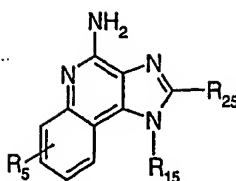
IV

5 wherein

R<sub>14</sub> is -CHR<sub>x</sub>R<sub>y</sub> wherein R<sub>y</sub> is hydrogen or a carbon-carbon bond, with the proviso that when R<sub>y</sub> is hydrogen R<sub>x</sub> is alkoxy of one to four carbon atoms, hydroxyalkoxy of one to four carbon atoms, 1-alkynyl of two to ten carbon atoms, tetrahydropyranyl, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms, 2-, 3-, or 4-pyridyl, and with the further proviso  
10 that when R<sub>y</sub> is a carbon-carbon bond R<sub>y</sub> and R<sub>x</sub> together form a tetrahydrofuranyl group optionally substituted with one or more substituents independently selected from the group consisting of hydroxy and hydroxyalkyl of one to four carbon atoms;

R<sub>24</sub> is selected from the group consisting of hydrogen, alkyl of one to four carbon atoms, phenyl, and substituted phenyl wherein the substituent is selected from the group  
15 consisting of alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen; and

R<sub>4</sub> is selected from the group consisting of hydrogen, straight chain or branched chain alkoxy containing one to four carbon atoms, halogen, and straight chain or branched  
20 chain alkyl containing one to four carbon atoms;

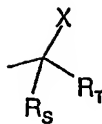


V

wherein

$R_{15}$  is selected from the group consisting of: hydrogen; straight chain or branched chain alkyl containing one to ten carbon atoms and substituted straight chain or branched chain alkyl containing one to ten carbon atoms, wherein the substituent is selected from the group consisting of cycloalkyl containing three to six carbon atoms and cycloalkyl containing three to six carbon atoms substituted by straight chain or branched chain alkyl containing one to four carbon atoms; straight chain or branched chain alkenyl containing two to ten carbon atoms and substituted straight chain or branched chain alkenyl containing two to ten carbon atoms, wherein the substituent is selected from the group consisting of cycloalkyl containing three to six carbon atoms and cycloalkyl containing three to six carbon atoms substituted by straight chain or branched chain alkyl containing one to four carbon atoms; hydroxyalkyl of one to six carbon atoms; alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to six carbon atoms; acyloxyalkyl wherein the acyloxy moiety is alkanoyloxy of two to four carbon atoms or benzoyloxy, and the alkyl moiety contains one to six carbon atoms; benzyl; (phenyl)ethyl; and phenyl; said benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently selected from the group consisting of alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen, with the proviso that when said benzene ring is substituted by two of said moieties, then the moieties together contain no more than six carbon atoms;

R<sub>25</sub> is



wherein

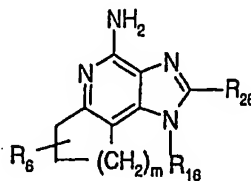
R<sub>S</sub> and R<sub>T</sub> are independently selected from the group consisting of hydrogen, alkyl  
5 of one to four carbon atoms, phenyl, and substituted phenyl wherein the substituent is  
selected from the group consisting of alkyl of one to four carbon atoms, alkoxy of one to  
four carbon atoms, and halogen;

X is selected from the group consisting of alkoxy containing one to four carbon  
atoms, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the  
10 alkyl moiety contains one to four carbon atoms, hydroxyalkyl of one to four carbon atoms,  
haloalkyl of one to four carbon atoms, alkylamido wherein the alkyl group contains one to  
four carbon atoms, amino, substituted amino wherein the substituent is alkyl or  
hydroxyalkyl of one to four carbon atoms, azido, chloro, hydroxy, 1-morpholino, 1-  
pyrrolidino, alkylthio of one to four carbon atoms; and

15 R<sub>S</sub> is selected from the group consisting of hydrogen, straight chain or branched  
chain alkoxy containing one to four carbon atoms, halogen, and straight chain or branched  
chain alkyl containing one to four carbon atoms;

and a pharmaceutically acceptable salt of any of the foregoing.

Preferred 6,7 fused cycloalkylimidazopyridine amine IRM compounds are defined by Formula VI below:



VI

5 wherein m is 1, 2, or 3;

$R_{16}$  is selected from the group consisting of hydrogen; cyclic alkyl of three, four, or five carbon atoms; straight chain or branched chain alkyl containing one to ten carbon atoms and substituted straight chain or branched chain alkyl containing one to ten carbon atoms, wherein the substituent is selected from the group consisting of cycloalkyl containing three to six carbon atoms and cycloalkyl containing three to six carbon atoms substituted by straight chain or branched chain alkyl containing one to four carbon atoms; fluoro- or chloroalkyl containing from one to ten carbon atoms and one or more fluorine or chlorine atoms; straight chain or branched chain alkenyl containing two to ten carbon atoms and substituted straight chain or branched chain alkenyl containing two to ten carbon atoms, wherein the substituent is selected from the group consisting of cycloalkyl containing three to six carbon atoms and cycloalkyl containing three to six carbon atoms substituted by straight chain or branched chain alkyl containing one to four carbon atoms; hydroxyalkyl of one to six carbon atoms; alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to six carbon atoms; acyloxyalkyl wherein the acyloxy moiety is alkanoyloxy of two to four carbon atoms or benzyloxy, and the alkyl moiety contains one to six carbon atoms, with the proviso that any such alkyl, substituted alkyl, alkenyl, substituted alkenyl, hydroxyalkyl, alkoxyalkyl, or acyloxyalkyl group does not have a fully carbon substituted carbon atom bonded

directly to the nitrogen atom; benzyl; (phenyl)ethyl; and phenyl; said benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently selected from the group consisting of alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen, with the proviso that when said  
5 benzene ring is substituted by two of said moieties, then the moieties together contain no more than six carbon atoms;

and  $-\text{CHR}_x\text{R}_y$

wherein

$\text{R}_y$  is hydrogen or a carbon-carbon bond, with the proviso that when  $\text{R}_y$  is hydrogen  
10  $\text{R}_x$  is alkoxy of one to four carbon atoms, hydroxyalkoxy of one to four carbon atoms, 1-alkynyl of two to ten carbon atoms, tetrahydropyranyl, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms, 2-, 3-, or 4-pyridyl, and with the further proviso that when  $\text{R}_y$  is a carbon-carbon bond  $\text{R}_y$  and  $\text{R}_x$  together form a tetrahydrofuranyl group optionally substituted with one or  
15 more substituents independently selected from the group consisting of hydroxy and hydroxyalkyl of one to four carbon atoms,

$\text{R}_{26}$  is selected from the group consisting of hydrogen, straight chain or branched chain alkyl containing one to eight carbon atoms, straight chain or branched chain hydroxyalkyl containing one to six carbon atoms, morpholinoalkyl, benzyl, (phenyl)ethyl  
20 and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by a moiety selected from the group consisting of methyl, methoxy, and halogen; and

$-\text{C}(\text{R}_S)(\text{R}_T)(\text{X})$  wherein  $\text{R}_S$  and  $\text{R}_T$  are independently selected from the group consisting of hydrogen, alkyl of one to four carbon atoms, phenyl, and substituted phenyl

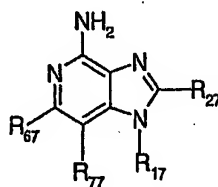


wherein the substituent is selected from the group consisting of alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen;

X is selected from the group consisting of alkoxy containing one to four carbon atoms, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms, haloalkyl of one to four carbon atoms, alkylamido wherein the alkyl group contains one to four carbon atoms, amino, substituted amino wherein the substituent is alkyl or hydroxyalkyl of one to four carbon atoms, azido, alkylthio of one to four carbon atoms, and morpholinoalkyl wherein the alkyl moiety contains one to four carbon atoms, and

R<sub>6</sub> is selected from the group consisting of hydrogen, fluoro, chloro, straight chain or branched chain alkyl containing one to four carbon atoms, and straight chain or branched chain fluoro- or chloroalkyl containing one to four carbon atoms and at least one fluorine or chlorine atom; and pharmaceutically acceptable salts thereof.

Preferred imidazopyridine amine IRM compounds are defined by Formula VII below:



VII

wherein

R<sub>17</sub> is selected from the group consisting of hydrogen; -CH<sub>2</sub>R<sub>w</sub> wherein R<sub>w</sub> is selected from the group consisting of straight chain, branched chain, or cyclic alkyl containing one to ten carbon atoms, straight chain or branched chain alkenyl containing

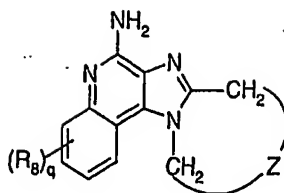
two to ten carbon atoms, straight chain or branched chain hydroxyalkyl containing one to six carbon atoms, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to six carbon atoms, and phenylethyl; and -  
 $\text{CH}=\text{CR}_Z\text{R}_Z$  wherein each  $\text{R}_Z$  is independently straight chain, branched chain, or cyclic alkyl of one to six carbon atoms;

$\text{R}_{27}$  is selected from the group consisting of hydrogen, straight chain or branched chain alkyl containing one to eight carbon atoms, straight chain or branched chain hydroxyalkyl containing one to six carbon atoms, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to six carbon atoms, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by a moiety selected from the group consisting of methyl, methoxy, and halogen; and morpholinoalkyl wherein the alkyl moiety contains one to four carbon atoms;

$\text{R}_{67}$  and  $\text{R}_{77}$  are independently selected from the group consisting of hydrogen and alkyl of one to five carbon atoms, with the proviso that  $\text{R}_{67}$  and  $\text{R}_{77}$  taken together contain no more than six carbon atoms, and with the further proviso that when  $\text{R}_{77}$  is hydrogen then  $\text{R}_{67}$  is other than hydrogen and  $\text{R}_{27}$  is other than hydrogen or morpholinoalkyl, and with the further proviso that when  $\text{R}_{67}$  is hydrogen then  $\text{R}_{77}$  and  $\text{R}_{27}$  are other than hydrogen;

and pharmaceutically acceptable salts thereof.

Preferred 1,2-bridged imidazoquinoline amine IRM compounds are defined by Formula VIII below:



VIII

wherein

Z is selected from the group consisting of:

5  $-(CH_2)_p-$  wherein p is 1 to 4;

$-(CH_2)_a-C(R_D R_E)(CH_2)_b-$ , wherein a and b are integers and a+b is 0 to 3,  $R_D$  is

hydrogen or alkyl of one to four carbon atoms, and  $R_E$  is selected from the group

consisting of alkyl of one to four carbon atoms, hydroxy,  $-OR_F$  wherein  $R_F$  is alkyl of one

to four carbon atoms, and  $-NR_G R'_G$  wherein  $R_G$  and  $R'_G$  are independently hydrogen or

10 alkyl of one to four carbon atoms; and

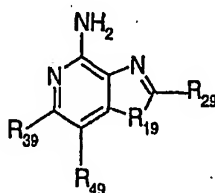
$-(CH_2)_a-(Y)-(CH_2)_b-$  wherein a and b are integers and a+b is 0 to 3, and Y is O, S,

or  $-NR_J-$  wherein  $R_J$  is hydrogen or alkyl of one to four carbon atoms;

and wherein q is 0 or 1 and  $R_8$  is selected from the group consisting of alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen,

15 and pharmaceutically acceptable salts thereof.

Suitable thiazolo- and oxazolo- quinolinamine and pyridinamine compounds include compounds of Formula IX:



IX

20 wherein:

$R_{19}$  is selected from the group consisting of oxygen, sulfur and selenium;

$R_{29}$  is selected from the group consisting of

-hydrogen;

-alkyl;

5

-alkyl-OH;

-haloalkyl;

-alkenyl;

-alkyl-X-alkyl;

-alkyl-X-alkenyl;

10

-alkenyl-X-alkyl;

-alkenyl-X-alkenyl;

-alkyl-N( $R_{59}$ )<sub>2</sub>;

-alkyl-N<sub>3</sub>;

-alkyl-O-C(O)-N( $R_{59}$ )<sub>2</sub>;

15

-heterocyclyl;

-alkyl-X-heterocyclyl;

-alkenyl-X-heterocyclyl;

-aryl;

-alkyl-X-aryl;

20

-alkenyl-X-aryl;

-heteroaryl;

-alkyl-X-heteroaryl; and

-alkenyl-X-heteroaryl;

$R_{39}$  and  $R_{49}$  are each independently:

-hydrogen;

-X-alkyl;

-halo;

-haloalkyl;

5 -N(R<sub>59</sub>)<sub>2</sub>;

or when taken together, R<sub>39</sub> and R<sub>49</sub> form a fused

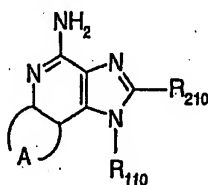
aromatic, heteroaromatic, cycloalkyl or heterocyclic ring;

X is selected from the group consisting of -O-, -S-, -NR<sub>59</sub>-, -C(O)-, -C(O)O-,  
-OC(O)-, and a bond; and

10 each R<sub>59</sub> is independently H or C<sub>1-8</sub>alkyl;

and pharmaceutically acceptable salts thereof.

Suitable imidazonaphthyridine and tetrahydroimidazonaphthyridine IRM  
compounds are those of Formulae X and XI below:



X

wherein

A is =N-CR=CR-CR=; =CR-N=CR-CR=; =CR-CR=N-CR=; or  
=CR-CR=CR-N=;

20 R<sub>110</sub> is selected from the group consisting of:

- hydrogen;

-C<sub>1-20</sub> alkyl or C<sub>2-20</sub> alkenyl that is unsubstituted or substituted by one or more  
substituents selected from the group consisting of:

-aryl;

-heteroaryl;

-heterocyclyl;

-O-C<sub>1-20</sub> alkyl,

5

-O-(C<sub>1-20</sub>alkyl)<sub>0-1</sub>-aryl;

-O-(C<sub>1-20</sub>alkyl)<sub>0-1</sub>-heteroaryl;

-O-(C<sub>1-20</sub>alkyl)<sub>0-1</sub>-heterocyclyl;

-C<sub>1-20</sub> alkoxycarbonyl;

-S(O)<sub>0-2</sub>-C<sub>1-20</sub> alkyl;

10

-S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-aryl;

-S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heteroaryl;

-S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heterocyclyl;

-N(R<sub>310</sub>)<sub>2</sub>;

-N<sub>3</sub>;

15

oxo;

-halogen;

-NO<sub>2</sub>;

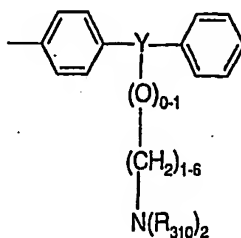
-OH; and

-SH; and

20

-C<sub>1-20</sub> alkyl-NR<sub>310</sub>-Q-X-R<sub>410</sub> or -C<sub>2-20</sub> alkenyl-NR<sub>310</sub>-Q-X-R<sub>410</sub> wherein Q is -CO- or -SO<sub>2</sub>-; X is a bond, -O- or -NR<sub>310</sub>- and R<sub>410</sub> is aryl; heteroaryl; heterocyclyl; or -C<sub>1-20</sub> alkyl or C<sub>2-20</sub> alkenyl that is unsubstituted or substituted by one or more substituents selected from the group consisting of:

- aryl;  
 -heteroaryl;  
 -heterocyclyl;  
 -O-C<sub>1-20</sub> alkyl,  
 5 -O-(C<sub>1-20</sub>alkyl)<sub>0-1</sub>-aryl;  
 -O-(C<sub>1-20</sub>alkyl)<sub>0-1</sub>-heteroaryl;  
 -O-(C<sub>1-20</sub>alkyl)<sub>0-1</sub>-heterocyclyl;  
 -C<sub>1-20</sub> alkoxycarbonyl;  
 -S(O)<sub>0-2</sub>-C<sub>1-20</sub> alkyl;  
 10 -S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-aryl;  
 -S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heteroaryl;  
 -S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heterocyclyl;  
 -N(R<sub>310</sub>)<sub>2</sub>;  
 -NR<sub>310</sub>-CO-O-C<sub>1-20</sub>alkyl;  
 15 -N<sub>3</sub>;  
 oxo;  
 -halogen;  
 -NO<sub>2</sub>;  
 -OH; and  
 20 -SH; or R<sub>410</sub> is



wherein Y is -N- or -CR-;

R<sub>210</sub> is selected from the group consisting of:

-hydrogen;

-C<sub>1-10</sub> alkyl;

5 -C<sub>2-10</sub> alkenyl;

-aryl;

-C<sub>1-10</sub> alkyl -O-C<sub>1-10</sub>-alkyl;

-C<sub>1-10</sub> alkyl-O-C<sub>2-10</sub> alkenyl; and

-C<sub>1-10</sub> alkyl or C<sub>2-10</sub> alkenyl substituted by one or more substituents selected from

10 the group consisting of:

-OH;

-halogen;

-N(R<sub>310</sub>)<sub>2</sub>;

-CO-N(R<sub>310</sub>)<sub>2</sub>;

15 -CO-C<sub>1-10</sub> alkyl;

-N<sub>3</sub>;

-aryl;

-heteroaryl;

-heterocyclyl;

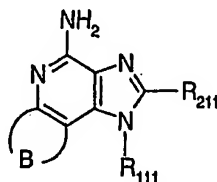
20 -CO-aryl; and

-CO-heteroaryl;

each R<sub>310</sub> is independently selected from the group consisting of hydrogen and C<sub>1-10</sub> alkyl; and



each R is independently selected from the group consisting of hydrogen,  
 $C_{1-10}$  alkyl,  $C_{1-10}$  alkoxy, halogen and trifluoromethyl,  
 and pharmaceutically acceptable salts thereof.



5

XI

wherein

B is  $-NR-C(R)_2-C(R)_2-C(R)_2-$ ;  $-C(R)_2-NR-C(R)_2-C(R)_2-$ ;  
 $-C(R)_2-C(R)_2-NR-C(R)_2-$  or  $-C(R)_2-C(R)_2-C(R)_2-NR-$ ;

$R_{111}$  is selected from the group consisting of:

10

- hydrogen;

$-C_{1-20}$  alkyl or  $C_{2-20}$  alkenyl that is unsubstituted or substituted by one or more  
 substituents selected from the group consisting of:

-aryl;

-heteroaryl;

15

-heterocyclyl;

$-O-C_{1-20}$  alkyl;

$-O-(C_{1-20}\text{alkyl})_{0-1}$ -aryl;

$-O-(C_{1-20}\text{alkyl})_{0-1}$ -heteroaryl;

$-O-(C_{1-20}\text{alkyl})_{0-1}$ -heterocyclyl;

20

$-C_{1-20}$  alkoxycarbonyl;

$-S(O)_{0-2}-C_{1-20}$  alkyl;

$-S(O)_{0-2}-(C_{1-20}\text{alkyl})_{0-1}$ -aryl;

$-\text{S}(\text{O})_{0-2}-(\text{C}_{1-20} \text{ alkyl})_{0-1}\text{-heteroaryl};$   
 $-\text{S}(\text{O})_{0-2}-(\text{C}_{1-20} \text{ alkyl})_{0-1}\text{-heterocyclyl};$   
 $-\text{N}(\text{R}_{311})_2;$   
 $-\text{N}_3;$   
 5       $\text{oxo};$   
 $-\text{halogen};$   
 $-\text{NO}_2;$   
 $-\text{OH};$  and  
 $-\text{SH};$  and

10

$-\text{C}_{1-20} \text{ alkyl}-\text{NR}_{311}-\text{Q}-\text{X}-\text{R}_{411}$  or  $-\text{C}_{2-20} \text{ alkenyl}-\text{NR}_{311}-\text{Q}-\text{X}-\text{R}_{411}$  wherein **Q** is  $-\text{CO}-$  or  $-\text{SO}_2-$ ; **X** is a bond,  $-\text{O}-$  or  $-\text{NR}_{311}-$  and **R**<sub>411</sub> is aryl; heteroaryl; heterocyclyl; or  $-\text{C}_{1-20} \text{ alkyl}$  or  $\text{C}_{2-20} \text{ alkenyl}$  that is unsubstituted or substituted by one or more substituents selected from the group consisting of:

15

$-\text{aryl};$   
 $-\text{heteroaryl};$   
 $-\text{heterocyclyl};$   
 $-\text{O}-\text{C}_{1-20} \text{ alkyl},$   
 $-\text{O}-(\text{C}_{1-20} \text{ alkyl})_{0-1}\text{-aryl};$

20

$-\text{O}-(\text{C}_{1-20} \text{ alkyl})_{0-1}\text{-heteroaryl};$   
 $-\text{O}-(\text{C}_{1-20} \text{ alkyl})_{0-1}\text{-heterocyclyl};$   
 $-\text{C}_{1-20} \text{ alkoxycarbonyl};$   
 $-\text{S}(\text{O})_{0-2}-\text{C}_{1-20} \text{ alkyl};$   
 $-\text{S}(\text{O})_{0-2}-(\text{C}_{1-20} \text{ alkyl})_{0-1}\text{-aryl};$

-S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heteroaryl;

-S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heterocyclyl;

-N(R<sub>311</sub>)<sub>2</sub>;

-NR<sub>311</sub>-CO-O-C<sub>1-20</sub>alkyl;

5

-N<sub>3</sub>;

oxo;

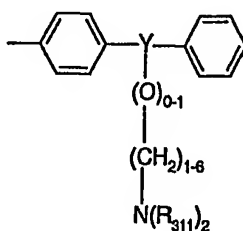
-halogen;

-NO<sub>2</sub>;

-OH; and

10

-SH; or R<sub>411</sub> is



wherein Y is -N- or -CR-;

R<sub>211</sub> is selected from the group consisting of:

-hydrogen;

15

-C<sub>1-10</sub> alkyl;

-C<sub>2-10</sub> alkenyl;

-aryl

-C<sub>1-10</sub> alkyl -O-C<sub>1-10</sub>-alkyl;

-C<sub>1-10</sub> alkyl-O-C<sub>2-10</sub> alkenyl; and

20

-C<sub>1-10</sub> alkyl or C<sub>2-10</sub> alkenyl substituted by one or more substituents selected from

the group consisting of:

-OH;

-halogen;

-N(R<sub>311</sub>)<sub>2</sub>;

-CO-N(R<sub>311</sub>)<sub>2</sub>;

5 -CO-C<sub>1-10</sub> alkyl;

-N<sub>3</sub>;

-aryl;

-heteroaryl;

-heterocyclyl;

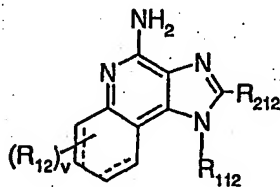
10 -CO-aryl; and

-CO-heteroaryl;

each R<sub>311</sub> is independently selected from the group consisting of hydrogen and C<sub>1-10</sub> alkyl; and

each R is independently selected from the group consisting of hydrogen,  
15 C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy, halogen and trifluoromethyl,  
and pharmaceutically acceptable salts thereof.

Additional preferred 1*H*-imidazo[4,5-*c*]quinolin-4-amines and tetrahydro- 1*H*-imidazo[4,5-*c*]quinolin-4-amines include compounds defined by Formulas XII, XIII and XIV below:



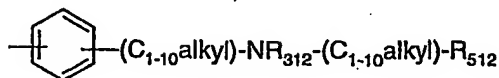
XII

wherein

$R_{112}$  is -alkyl- $NR_{312}$ -CO- $R_{412}$  or -alkenyl- $NR_{312}$ -CO- $R_{412}$  wherein  $R_{412}$  is aryl, heteroaryl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of:

- 5                   -alkyl;
- alkenyl;
- alkynyl;
- (alkyl)<sub>0-1</sub>-aryl;
- (alkyl)<sub>0-1</sub>-(substituted aryl);
- 10                  -(alkyl)<sub>0-1</sub>-heteroaryl;
- (alkyl)<sub>0-1</sub>-(substituted heteroaryl);
- O-alkyl;
- O-(alkyl)<sub>0-1</sub>-aryl;
- O-(alkyl)<sub>0-1</sub>-(substituted aryl);
- 15                  -O-(alkyl)<sub>0-1</sub>-heteroaryl;
- O-(alkyl)<sub>0-1</sub>-(substituted heteroaryl);
- CO-aryl;
- CO-(substituted aryl);
- CO-heteroaryl;
- 20                  -CO-(substituted heteroaryl);
- COOH;
- CO-O-alkyl;
- CO-alkyl;
- S(O)<sub>0-2</sub>-alkyl;
- 25                  -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-aryl;
- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted aryl);
- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heteroaryl;
- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted heteroaryl);
- P(O)(OR<sub>312</sub>)<sub>2</sub>;
- 30                  -NR<sub>312</sub>-CO-O-alkyl;
- N<sub>3</sub>;
- halogen;

-NO<sub>2</sub>;  
 -CN;  
 -haloalkyl;  
 -O-haloalkyl;  
 -CO-haloalkyl;  
 -OH;  
 -SH; and in the case of alkyl, alkenyl, or heterocyclyl, oxo;  
 or R<sub>412</sub> is



wherein R<sub>512</sub> is an aryl, (substituted aryl), heteroaryl, (substituted heteroaryl),  
 heterocyclyl or (substituted heterocyclyl) group;

R<sub>212</sub> is selected from the group consisting of:

-hydrogen;  
 -alkyl;  
 -alkenyl;  
 -aryl;  
 -(substituted aryl);  
 -heteroaryl;  
 -(substituted heteroaryl);  
 -heterocyclyl;  
 -(substituted heterocyclyl);  
 -alkyl -O-alkyl;  
 -alkyl-O-alkenyl; and  
 -alkyl or alkenyl substituted by one or more substituents selected from the

group consisting of:

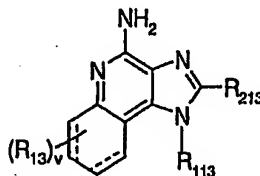
-OH;  
 -halogen;  
 -N(R<sub>312</sub>)<sub>2</sub>;  
 -CO-N(R<sub>312</sub>)<sub>2</sub>;  
 -CO-C<sub>1-10</sub> alkyl;

-CO-O-C<sub>1-10</sub> alkyl;  
 -N<sub>3</sub>;  
 -aryl;  
 -(substituted aryl);  
 5 -heteroaryl;  
 -(substituted heteroaryl);  
 -heterocyclyl;  
 -(substituted heterocyclyl);  
 -CO-aryl; and  
 10 -CO-heteroaryl;

each R<sub>312</sub> is independently selected from the group consisting of hydrogen; C<sub>1-10</sub> alkyl-heteroaryl; C<sub>1-10</sub> alkyl-(substituted heteroaryl); C<sub>1-10</sub> alkyl-aryl; C<sub>1-10</sub> alkyl-(substituted aryl) and C<sub>1-10</sub> alkyl;

v is 0 to 4;

15 and each R<sub>12</sub> present is independently selected from the group consisting of C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy, halogen and trifluoromethyl;



XIII

20 wherein

R<sub>113</sub> is -alkyl-NR<sub>313</sub>-SO<sub>2</sub>-X-R<sub>413</sub> or -alkenyl-NR<sub>313</sub>-SO<sub>2</sub>-X-R<sub>413</sub>;

X is a bond or -NR<sub>513</sub>-;

R<sub>413</sub> is aryl, heteroaryl, heterocyclyl, alkyl or alkenyl, each of which may be  
 25 unsubstituted or substituted by one or more substituents selected from the group consisting of:

-alkyl;

- alkenyl;
- aryl;
- heteroaryl;
- heterocyclyl;
- 5 -substituted cycloalkyl;
- substituted aryl;
- substituted heteroaryl;
- substituted heterocyclyl;
- O-alkyl;
- 10 -O-(alkyl)<sub>0-1</sub>-aryl;
- O-(alkyl)<sub>0-1</sub>-substituted aryl;
- O-(alkyl)<sub>0-1</sub>-heteroaryl;
- O-(alkyl)<sub>0-1</sub>-substituted heteroaryl;
- O-(alkyl)<sub>0-1</sub>-heterocyclyl;
- 15 -O-(alkyl)<sub>0-1</sub>-substituted heterocyclyl;
- COOH;
- CO-O-alkyl;
- CO-alkyl;
- S(O)<sub>0-2</sub>-alkyl;
- 20 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-aryl;
- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-substituted aryl;
- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heteroaryl;
- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-substituted heteroaryl;
- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heterocyclyl;
- 25 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-substituted heterocyclyl;
- (alkyl)<sub>0-1</sub>-NR<sub>313</sub>R<sub>313</sub>;
- (alkyl)<sub>0-1</sub>-NR<sub>313</sub>-CO-O-alkyl;
- (alkyl)<sub>0-1</sub>-NR<sub>313</sub>-CO-alkyl;
- (alkyl)<sub>0-1</sub>-NR<sub>313</sub>-CO-aryl;
- 30 -(alkyl)<sub>0-1</sub>-NR<sub>313</sub>-CO-substituted aryl;
- (alkyl)<sub>0-1</sub>-NR<sub>313</sub>-CO-heteroaryl;
- (alkyl)<sub>0-1</sub>-NR<sub>313</sub>-CO-substituted heteroaryl;



- 5                    -N<sub>3</sub>;  
                    -halogen;  
                    -haloalkyl;  
                    -haloalkoxy;  
                    -CO-haloalkyl;  
                    -CO-haloalkoxy;  
                    -NO<sub>2</sub>;  
                    -CN;  
                    -OH;  
10                   -SH; and in the case of alkyl, alkenyl, or heterocyclyl, oxo;

R<sub>213</sub> is selected from the group consisting of:

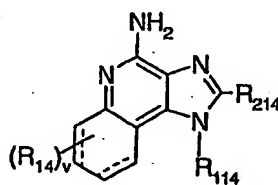
- 15                   -hydrogen;  
                    -alkyl;  
                    -alkenyl;  
                    -aryl;  
                    -substituted aryl;  
                    -heteroaryl;  
                    -substituted heteroaryl;  
20                   -alkyl-O-alkyl;  
                    -alkyl-O-alkenyl; and  
                    -alkyl or alkenyl substituted by one or more substituents selected from the  
                    group consisting of:

- 25                   -OH;  
                    -halogen;  
                    -N(R<sub>313</sub>)<sub>2</sub>;  
                    -CO-N(R<sub>313</sub>)<sub>2</sub>;  
                    -CO-C<sub>1-10</sub> alkyl;  
                    -CO-O-C<sub>1-10</sub> alkyl;  
30                   -N<sub>3</sub>;  
                    -aryl;  
                    -substituted aryl;

-heteroaryl;  
 -substituted heteroaryl;  
 -heterocyclyl;  
 -substituted heterocyclyl;  
 -CO-aryl;  
 -CO-(substituted aryl);  
 -CO-heteroaryl; and  
 -CO-(substituted heteroaryl);

each  $R_{313}$  is independently selected from the group consisting of hydrogen and  $C_{1-10}$  alkyl;

$R_{513}$  is selected from the group consisting of hydrogen and  $C_{1-10}$  alkyl, or  $R_{413}$  and  $R_{513}$  can combine to form a 3 to 7 membered heterocyclic or substituted heterocyclic ring;  
 $v$  is 0 to 4 and each  $R_{13}$  present is independently selected from the group consisting of  $C_{1-10}$  alkyl,  $C_{1-10}$  alkoxy, halogen and trifluoromethyl;



XIV

wherein

$R_{114}$  is -alkyl-NR<sub>314</sub>-CY-NR<sub>514</sub>-X-R<sub>414</sub> or  
 -alkenyl-NR<sub>314</sub>-CY- NR<sub>514</sub>-X- R<sub>414</sub>

wherein

Y is =O or =S;

X is a bond, -CO- or -SO<sub>2</sub>-;

$R_{414}$  is aryl, heteroaryl, heterocyclyl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of:

-alkyl;

- alkenyl;
- aryl;
- heteroaryl;
- heterocyclyl;
- 5 -substituted aryl;
- substituted heteroaryl;
- substituted heterocyclyl;
- O-alkyl;
- O-(alkyl)<sub>0-1</sub>-aryl;
- 10 -O-(alkyl)<sub>0-1</sub>-substituted aryl;
- O-(alkyl)<sub>0-1</sub>-heteroaryl;
- O-(alkyl)<sub>0-1</sub>-substituted heteroaryl;
- O-(alkyl)<sub>0-1</sub>-heterocyclyl;
- O-(alkyl)<sub>0-1</sub>-substituted heterocyclyl;
- 15 -COOH;
- CO-O-alkyl;
- CO-alkyl;
- S(O)<sub>0-2</sub>-alkyl;
- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-aryl;
- 20 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-substituted aryl;
- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heteroaryl;
- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-substituted heteroaryl;
- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heterocyclyl;
- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-substituted heterocyclyl;
- 25 -(alkyl)<sub>0-1</sub>-NR<sub>314</sub>R<sub>314</sub>;
- (alkyl)<sub>0-1</sub>-NR<sub>314</sub>-CO-O-alkyl;
- (alkyl)<sub>0-1</sub>-NR<sub>314</sub>-CO-alkyl;
- (alkyl)<sub>0-1</sub>-NR<sub>314</sub>-CO-aryl;
- (alkyl)<sub>0-1</sub>-NR<sub>314</sub>-CO-substituted aryl;
- 30 -(alkyl)<sub>0-1</sub>-NR<sub>314</sub>-CO-heteroaryl;
- (alkyl)<sub>0-1</sub>-NR<sub>314</sub>-CO-substituted heteroaryl;
- N<sub>3</sub>;

-halogen;

-haloalkyl;

-haloalkoxy;

-CO-haloalkoxy;

5

-NO<sub>2</sub>;

-CN;

-OH;

-SH; and, in the case of alkyl, alkenyl or heterocyclyl, oxo;

with the proviso that when X is a bond R<sub>414</sub> can additionally be hydrogen;

10

R<sub>214</sub> is selected from the group consisting of:

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

15

-substituted aryl;

-heteroaryl;

-substituted heteroaryl;

-alkyl -O-alkyl;

-alkyl-O-alkenyl; and

20

-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;

-halogen;

-N(R<sub>314</sub>)<sub>2</sub>;

25

-CO-N(R<sub>314</sub>)<sub>2</sub>;

-CO-C<sub>1-10</sub> alkyl;

-CO-O-C<sub>1-10</sub> alkyl;

-N<sub>3</sub>;

-aryl;

30

-substituted aryl;

-heteroaryl;

-substituted heteroaryl;

-heterocyclyl;  
 -substituted heterocyclyl;  
 -CO-aryl;  
 -CO-(substituted aryl);  
 -CO-heteroaryl; and  
 -CO-(substituted heteroaryl);

5

each  $R_{314}$  is independently selected from the group consisting of hydrogen and  $C_{1-10}$  alkyl;

$R_{514}$  is selected from the group consisting of hydrogen and  $C_{1-10}$  alkyl, or  $R_{414}$  and  $R_{514}$  can combine to form a 3 to 7 membered heterocyclic or substituted heterocyclic ring;  
 10  $v$  is 0 to 4 and each  $R_{14}$  present is independently selected from the group consisting of  $C_{1-10}$  alkyl,  $C_{1-10}$  alkoxy, halogen and trifluoromethyl, and a pharmaceutically acceptable salts thereof.

Particularly preferred compounds include 1-(2-methylpropyl)-1*H*-imidazo[4,5-  
 15 *c*]quinolin-4-amine (imiquimod), 4-amino-2-ethoxymethyl- $\alpha,\alpha$ -dimethyl-1*H*-imidazo[4,5-  
*c*]quinoline-1-ethanol (resiquimod), 2-propyl[1,3]thiazolo[4,5-*c*]quinolin-4-amine, N-[4-  
 (4-amino-2-butyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butyl]-N'-cyclohexylurea; 2-  
 methyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine, and 1-(2-  
 methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine.

20 The pharmaceutical compositions can be provided in a form suitable for systemic application or in a form suitable for local delivery to the affected site. The latter mode is presently preferred. The pharmaceutical compositions can be formulated to provide for delivery of the IRM compound to the treatment site at a predetermined rate, for a predetermined duration, alone, or in combination with other therapeutic or prophylactic  
 25 agents, for example antibiotics, fluoride sources etc. Excipients commonly used to formulate drugs into a suitable vehicle can be incorporated as necessary provided that the excipient does not substantially interfere with the function or stability of the composition.

Non-limiting examples of forms suitable for the pharmaceutical compositions include enhanced viscosity formulations such as disclosed in U.S. Patent Nos. 5,939,047 and 6,123,957; transmucosal patches such as disclosed in U.S. Patent Nos. 5,780,045 and 5,750,134 and PCT Publication WO 00/19987; microcapsules such as disclosed in U.S.

5 Patent No. 5,500,228; biodegradable cross-linked hydrolyzed gelatin matrices such as those used in the PerioChip<sup>TM</sup> (available from Perio Products Ltd., Jerusalem, Israel); dental rinses and dentifrices. Excipients such as flavorings, colorants, surfactants, binders can be employed as needed.

10 A "treatment site" means the site where the pharmaceutical composition is delivered to the patient. Treatment sites are typically local sites proximate to a lesion and generally include the gingival surfaces, periodontal pockets, or any other site that the drug could be delivered to the maxillary or mandibular tissue. The composition is typically delivered topically or by placing the composition in the subgingival space (periodontal pocket).

15 As used herein, the term "therapeutically effective amount" means an amount of an IRM compound sufficient to prevent, reduce or reverse periodontal disease. The therapeutically effective amount of an IRM compound for periodontitis will vary depending on such things as the activity of the particular compound, the particular composition administered, the duration of delivery, the frequency of administration, the  
20 treatment site, and any other therapeutic agents being coadministered.

In general, a pharmaceutical composition useful for practicing the methods of the invention can contain from about 0.001% to 5.0% of an IRM compound based on total weight of the pharmaceutical composition. Typically the composition will contain from about 0.01% to 1% of an IRM compound.

The IRM compound may be present in the pharmaceutical composition as the sole therapeutically active ingredient or in combination with other therapeutic agents such as antibiotics, e.g., penicillins, tetracycline; antiseptics, e.g., chlorhexidine; corticosteroids, e.g., hydrocortisone, betamethasone; nonsteroidal antiinflammatories, e.g., flurbiprofen, ibuprofen, naproxen.

The frequency and duration of administration can vary as needed for prevention or treatment of the disease. Treatment regimens may include administration at least one time per week, typically two to three times per week, or even daily for at least one week, typically two weeks and in some cases three to four weeks. The patient can be rechecked according to the common standards of care. Thus recalls can be monthly, every two months and typically every three months. Repeated administration can be provided as needed.

Typically, the IRM compound can be applied to a treatment site in some type of sustained release formulation, such as gels, capsules, patches, biodegradable matrices, etc. for delivery of the IRM compound to the treatment site over a period of about 1-24 hours, typically about 1-8 hours, and in some embodiments, about 1-3 hours. It is also foreseen that in certain situations, a burst of IRM compound can be provided by direct administration, such as by subgingival placement, use of a dentifrice or mouth wash, etc. at the discretion of the clinician.

The following Examples are provided to further explain the invention through specific description of some embodiments of the invention. The Examples, however, are not intended to limit the scope of the invention.

### Example 1

#### Treatment of Mice with an IRM

Studies in mice infected with bacteria known to cause periodontitis were performed to determine the potential utility of the IRM compounds in this disease.

#### 5 Preparation and Maintenance of Bacterial Cultures

An isolate of *Porphyromonas gingivalis* from the subgingival pocket of a patient with adult periodontitis and non-insulin dependent diabetes was used. The isolate is deposited with American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209 USA as ATCC Accession No. 53977 (strain A7A1-28). The organisms were propagated in an anaerobic jar (Becton Dickinson Microbiology Systems, Cockeysville, MD) under an atmosphere of 5% CO<sub>2</sub> 10% H<sub>2</sub> and 85% N<sub>2</sub> at 37°C on PRAS (prereduced anaerobically sterilized) Brucella agar plates (Anaerobe Systems, Morgan Hill, CA).

10 Broth cultures were grown in BHTS media, a 50% mixture of Trypticase Soy and Brain Heart Infusion broth supplemented with 5% Yeast Extract (all from Becton Dickinson Microbiology Systems), 10µg/L hemin, 1µg/L metadione and 5% horse serum (Sigma Chemical, St. Louis, MO). Species were maintained by weekly transfer on plates. Frozen stocks were made by re-suspending log-phase cultures in 15% glycerol in BHTS and maintaining at -70°C for several months.

#### 15 Oral Infection of Mice with *Porphyromonas gingivalis*

20 90 conventional BALB/c specific pathogen-free mice (Charles River Labs, Wilmington, MA) were divided into three groups of about 30 mice per group. As shown in Table 1, Groups II and III, but not I, were infected with *P. gingivalis* as described below. Groups I and II were administered an IRM compound as described below.



Table 1. Experimental Protocol

Group/Treatment	Infected with <i>P.gingivalis</i>
I / IRM	NO
II / IRM	YES
III / NONE	YES

All mice were kept in an animal colony, where they were caged away from other animals. All mice were kept on a 12-hour light/dark cycle and received distilled water ad libitum. Mice within experiments were sex- and age-matched (12-18 weeks at the start of various experiments).

The mice in Groups I-III were given sulphamethoxazole/trimethoprim, 10 ml per pint in deionized water, ad libitum for 10 days before experimentation, followed by 4 days without antibiotics. The mice of Groups II-III were then infected by gavage with  $10^9$  colony-forming units of live *P. gingivalis*, in 100  $\mu$ l of phosphate buffered saline (PBS) with 2% carboxymethylcellulose, three times at 2 to 4 day intervals as described in Klausen et al, "Two complementary methods of assessing periodontal bone level in rats", Scandinavian Journal of Dental Research, 97, 494-9 (1989).

As shown in FIG. 2, two weeks prior to infection there was no evidence of *P. gingivalis* in any of the subject animals, a result that continued up to infection. The proportion of *P. gingivalis* in samples collected the first week after infection reached about 2%. See below. It remained between 2% and 5% during the remainder of the experiment. There was no significant difference between the levels of *P. gingivalis* in the IRM treated or untreated animals at any point in the experiment.

#### Bacterial Isolation from Plaque of Infected Mice

Subgingival plaque samples were obtained from the molars of mice from all three groups using sterile fine paper points (Johnson and Johnson Dental Products Co. East

Windsor, NJ). The points were placed in 1 ml of water that was then tested for total bacteria and *P. gingivalis* levels by quantitative PCR similar to that described for *Bacteroides forsythus* in Shelburne et al, "Quantitation of *Bacteroides forsythus* in subgingival plaque: comparison of immunoassay and quantitative polymerase chain reaction", J. Microbial. Methods, 39:97-107 (2000).

#### Treatment with Resiquimod

The mice of Groups I and II were dosed by oral gavage twice weekly for seven weeks with either 1 mg/kg or 0.1 mg/kg of resiquimod (4-amino-2-ethoxymethyl- $\alpha$ , $\alpha$ -dimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol) in 100  $\mu$ l of PBS. Animals were sacrificed at 43 days after treatment began.

#### Measurement of Alveolar Bone Loss

Bone loss around the maxillary molars was assessed by a morphometric method developed for studies of bone loss in mice. Baker P.J., et al., "Oral infection with *Porphyromonas gingivalis* and induced alveolar bone loss in immunocompetent and severe combined immunodeficient mice," Arch. Oral Biol., 39(12):1035-40 (December 1994). Jaws were de-fleshed after a 5-minute treatment in boiling water at 15 p.s.i. (1.05 Kg/cm<sup>2</sup>), immersed overnight in 3% hydrogen peroxide, air-dried and stained with 1% methylene blue. The bone level, that is, the distance from the cemento-enamel junction (CEJ) to the alveolar bone crest on the maxillary molars, was measured under a dissecting microscope (x 30). Fourteen (14) measurements of the bone level were made per mouse. All measurements of bone level were done three times in a random fashion. Values for horizontal bone levels in  $\mu$ m per site were generated by computer analysis of calibrated lines from the CEJ to the alveolar bone crest image acquired by video camera.

#### Results

In animals treated with resiquimod there was substantially less bone loss than in untreated animals (FIG. 3), and the difference was significant at a level appropriate for this model ( $p < 0.01$ ). There was no difference between the animals treated with 1 mg/kg doses of resiquimod and those treated with 0.1 mg/kg.

5       Interestingly, there was no reduction in the levels of *P. gingivalis* in the plaque of the subject animals that correlated with the difference in bone loss or the treatment (or non-treatment) of the mice. This indicates that the reduction in bone loss is due to modification of some host response, not the elimination of the bacteria, although they are clearly required to initiate the disease.

10

### Example 2

#### **Treatment of Naturally Occurring Periodontal Disease in a Dog with an IRM gel composition**

15       One dog with naturally occurring periodontal disease was identified by clinical signs including Gingival Index (scored 0-3 by observation), Bleeding Index (scored 0-3 by observation, and Probing Depth (measured to the nearest mm using a North Carolina Probe). The animal was treated with a gel composition containing resiquimod, prepared as described below, in addition to the standard treatment of scaling and root planing.

20       Therapeutic efficacy was determined by a trained examiner measuring the aforementioned indicies around the affected teeth.

#### Preparation of IRM Gel Composition Containing the IRM Resiquimod

Propylene glycol (700 g) and the IRM resiquimod (4-amino-2-ethoxymethyl- $\alpha,\alpha$ -  
25       dimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol, 7.0 g) were added to a 1000 mL glass beaker. The resulting mixture was heated (about 56° C) with stirring until all of the resiquimod was dissolved. The resulting solution was added to the mixing bowl of a

ROSS LDM-4 mixer. Triacetin (11,963.0 g) was added to the mixing bowl and the resulting mixture was mixed for 10 minutes at 36 rpm. Colloidal silicon dioxide (1,330.0 g, AEROSIL® 200 from Degussa, Frankfurt, Germany) was added in five parts. After each addition the resulting mixture was mixed at ambient pressure for 1 to 2 minutes at 36 rpm and then under vacuum (about 18 in Hg;  $4.0 \times 10^4$  Pa) for about 9 minutes at 36 rpm. The sides of the mixing bowl and the mixing blades were scraped. The formulation was mixed under vacuum (about 17 in Hg;  $4.3 \times 10^4$  Pa) for about 10 minutes at 36 rpm. The resulting gel contained 0.05% resiquimod, 5.0% propylene glycol, 9.5% colloidal silicon dioxide, and 85.45% triacetin.

10 Treatment with an IRM gel composition

The animal was sedated with xylazine at a dose of about 1mg/kg and its teeth cleaned of supragingival and subgingival plaque. The teeth affected by periodontitis were scaled and root planed to remove plaque and calculus from both supragingival (enamel) and subgingival (root) tooth surfaces using an ultrasonic Cavitron® (Dentsply, York, PA) and curets. The Cavitron was used to remove gross debris and the curets were used to smooth the root surface. A clean, smooth root surface resulting from the root planing allows epithelial and connective tissue attachment to the root surface during the healing process.

During the scaling procedure, there was no deliberate attempt to remove tooth substance along with the calculus. Root planing was performed to remove residual embedded calculus and portions of cementum from the roots of the teeth to produce a smooth, hard, clean surface. The primary objective of scaling and root planing is to restore gingival health by completely removing material from the tooth surface that provokes gingival inflammation; that is, plaque, calculus and altered cementum. Scaling

and root planing were not done as separate procedures in this Example. The difference between scaling and root planing is only a matter of degree. The nature of the tooth surface determines the degree to which the root surface is scaled or planed.

Depending on the size of the periodontitis lesion, about 10-50  $\mu$ l of the resiquimod gel composition prepared as described above was applied to sites affected by periodontitis. The composition was placed in the periodontal pocket adjacent to each site using a blunt 27 ga. needle and syringe filled with the composition. In this example a single application of the gel was used.

After treatment the animal was treated with yohimbine at about 0.1 mg/kg to reverse the sedation and the animal was returned to its cage.

#### Clinical Measurements

The pockets were examined at weekly intervals for the indices measured at the time of treatment. Measurement of attachment loss was performed using a standard North Carolina Periodontal probe marked at 1 mm intervals. The probe, which is about 1mm in diameter was inserted into the periodontal pocket to the base. The depth of the pocket (PD) was noted and the probe was withdrawn. The depth of the probe was noted at this time. At the same time the gingival index (GI) a measure of the redness of the gingival tissue (0=no redness to 3=very red, distended) was noted along with the bleeding index (BI) which is a measurement of the tendency of the pocket to bleed upon probing (0=no bleeding to 3=substantial bleeding). These are all standard measurements in dental practice for the evaluation of human periodontal disease.

#### Results

Referring to FIGs. 4a and 4b, there was an over all improvement in PD, BI and GI as a result of the mechanical cleaning of the teeth (compare left hand panels of Baseline

graph (FIG. 4a) and 2 Week Post-Treatment graph (FIG. 4b). There was improvement in the BI and GI of the treated sites compared to untreated sites that is statistically significant ( $p < 0.01$ ). (Compare left and right panels of the 2 Week Post-Treatment graph, FIG. 4b). This is due to the IRM treatment.

5           There was no significant difference in the PD of the treated compared to untreated sites (compare left and right panels of 2 Week Post-Treatment graph, FIG. 4b). The inventors believe this is due to two-weeks being an insufficient time post-treatment for rebuilding the tooth attachment cellular apparatus.

The study was not a terminal study and thus bone loss was not determined

10

### Example 3

#### **Treatment of Chronic Adult Periodontal Disease in a Human Patient with an IRM Containing Transmucosal Patch**

15           A human patient affected with chronic adult periodontal disease can be identified by clinical signs typically including BI, GI, Probing Depth. The human can be treated with a transmucosal patch containing an IRM, prepared as described in Example 4 below, in addition to the standard treatment of scaling and root planing.

20           The patient's teeth can be cleaned of supragingival plaque. The teeth affected by periodontitis can be scaled and root planed to remove plaque and calculus from both supragingival and subgingival tooth surfaces using known instruments, such as, for example, an ultrasonic Cavitron and curets. The Cavitron is used to remove gross debris and the curets are used to smooth the root surface

25           Depending on the size of the periodontitis lesion, a transmucosal patch containing about 0.05 – 1.0 % of IRM per patch, and prepared, for example, as described in Example 4 below, can be adhered to the patient's gingiva proximate the sites affected by

periodontitis. The transmucosal patches can remain adhered to the gingiva for about 1-24 hours. In a typical situation the patch will remain adhered for about 1-3 hours. The patches can be applied two times a week for three weeks. The patient can be reexamined at 1 month after completion of treatment and at three month intervals thereafter.

- 5 Treatment can be repeated as necessary.

#### Example 4

##### **Preparation of a Transmucosal Patch Containing the IRM 4-amino-2-ethoxymethyl- $\alpha,\alpha$ -dimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol**

- 10 A transmucosal patch suitable for gingival application was prepared containing the IRM compound 4-amino-2-ethoxymethyl- $\alpha,\alpha$ -dimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol (resiquimod).

- Isooctyl acrylate (20.03 g), acrylic acid (19.98 g), methoxy polyethylene glycol 550 monomethacrylate (19.07 g), polyethylene glycol 400 diacrylate (0.72 g), polyacrylic acid (5.73 g of a solution containing 17.5% by weight of polyacrylic acid in water),  
15 polyoxyethylene 10 oleyl ether (21.78 g of Brij<sup>®</sup> 97), propylene glycol (10.00), water (2.89 g), resiquimod (0.10 g) and 2-hydroxy-1-(4-(2-hydroxyethoxy)phenyl)-2-methyl-1-propanone (0.55 g of Irgacure<sup>®</sup> 2959) were combined in a glass jar and then mixed on a platform shaker until a clear liquid composition was obtained. The composition contained  
20 0.10% by weight of resiquimod.

- The liquid was knife coated at a wet thickness of 25 mil (635  $\mu$ M) onto the non-woven polypropylene side of a trilaminate backing and the exposed surface was covered with a clear polyester (1.5 mil, 38  $\mu$ M) silicone coated release liner. The coated composition was then exposed to UVA light for 8 minutes so that the composition was  
25 exposed to a total energy of 2677 mJ/cm<sup>2</sup>. The release liner was removed and the exposed

surface of the cured composition was laminated to a silicone coated polyester release liner ( 5mil, 127  $\mu$ M). Patches (2.05 cm<sup>2</sup>) were cut from the laminate.

From the foregoing detailed description and examples, it will be evident that  
5 modifications and variations can be made in the methods of the invention without  
departing from the spirit or scope of the invention. Therefore, it is intended that all  
modifications and variations not departing from the spirit of the invention come within the  
scope of the claims and their equivalents.



## WHAT IS CLAIMED IS:

1. Use of an immune response modifier (IRM) compound in the manufacture of a pharmaceutical formulation for the treatment or prevention of periodontal disease wherein the formulation is applied directly to periodontal tissue in a patient affected by the periodontal condition.
2. The use according to claim 1 wherein the IRM compound is selected from the group of immune response modifiers comprising imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, oxazoloquinoline amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines.
3. The use according to claim 2 wherein the IRM is selected from the group consisting of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine; 4-amino-2-ethoxymethyl- $\alpha,\alpha$ -dimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol; 2-propyl[1,3]thiazolo[4,5-*c*]quinolin-4-amine; N-[4-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butyl]-N'-cyclohexylurea; 2-methyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine; and 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine.
4. The use according to claim 3 wherein the IRM is 4-amino-2-ethoxymethyl- $\alpha,\alpha$ -1*H*-imidazo[4,5-*c*]quinoline-1-ethanol.

5. The use according to claim 1 wherein the pharmaceutical formulation is in the form of a biodegradable matrix, a gel, a liquid, microcapsules, a mouth rinse, a paste, a semi-solid, a transmucosal patch or in a combination of these forms.

5 6. The use according to claim 1 wherein the pharmaceutical formulation is a gel formulation.

7. The use according to claim 1 wherein the pharmaceutical formulation is in the form of a transmucosal patch.

10

8. The use according to claim 6 wherein the pharmaceutical formulation is administered by application of the gel formulation to the periodontal pocket.

9. The use according to claim 6 wherein the pharmaceutical formulation is administered by application of the gel formulation to the patient's gingiva.

15

10. The use according to claim 7 wherein the pharmaceutical formulation is administered by applying the transmucosal patch to the patient's gingiva.

20 11. The use according to claim 10 wherein the transmucosal patch contains 0.05 to 0.1% of the IRM compound, based on total patch weight.

12. The use according to claim 10 wherein the transmucosal patch is applied to the patient's gingiva for about 1-3 hours.

25

13. The use according to claim 10 wherein more than one transmucosal patch is applied to the patient's gingiva.
14. The use according to claim 1 wherein the periodontal tissue is the gingiva.
- 5
15. The use according to claim 1 wherein the periodontal disease is periodontitis.
16. The use according to claim 15 wherein the periodontitis is chronic adult periodontitis.
- 10
17. The use according to claim 15 wherein the periodontitis is early onset periodontitis.
18. The use of claim 1 wherein the pharmaceutical formulation is coadministered with a therapeutic agent selected from the group consisting of antibiotics, antiseptics, corticosteroids, and nonsteroidal antiinflammatories.
- 15
19. Use of an immune response modifier (IRM) compound in the manufacture of a pharmaceutical formulation for the treatment of periodontal disease wherein the formulation is applied directly to periodontal tissue in a patient affected by the periodontal condition and wherein the formulation modulates the patient's immune response.
- 20

20. The use according to claim 19 wherein the formulation modulates the patient's TH2 immune response.

21. The use according to claim 19 wherein the formulation modulates the patient's TH1 immune response.

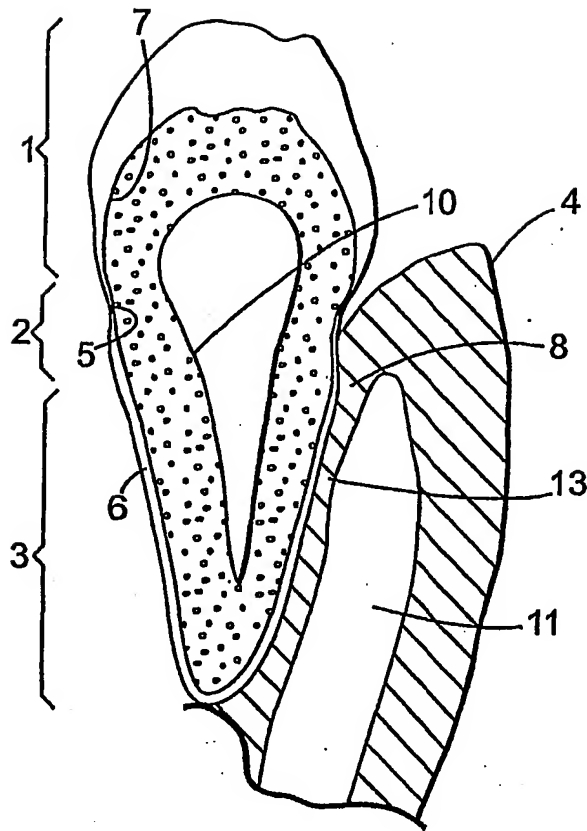
22. The use according to claim 19 wherein the pharmaceutical formulation includes an immune response modifier compound selected from the group of immune response modifiers comprising imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, oxazoloquinoline amines, thiazoloquinoline amines and 1,2-bridged imidazoquinoline amines.

23. The use according to claim 19 wherein the IRM is selected from the group consisting of 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine; 4-amino-2-ethoxymethyl- $\alpha,\alpha$ -dimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol; 2-propyl[1,3]thiazolo[4,5-*c*]quinolin-4-amine; N-[4-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)butyl]-N'-cyclohexylurea; 2-methyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine; and 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine.

24. The use according to claim 23 wherein the immune response modifier compound is 4-amino-2-ethoxymethyl- $\alpha,\alpha$ -1*H*-imidazo[4,5-*c*]quinoline-1-ethanol.

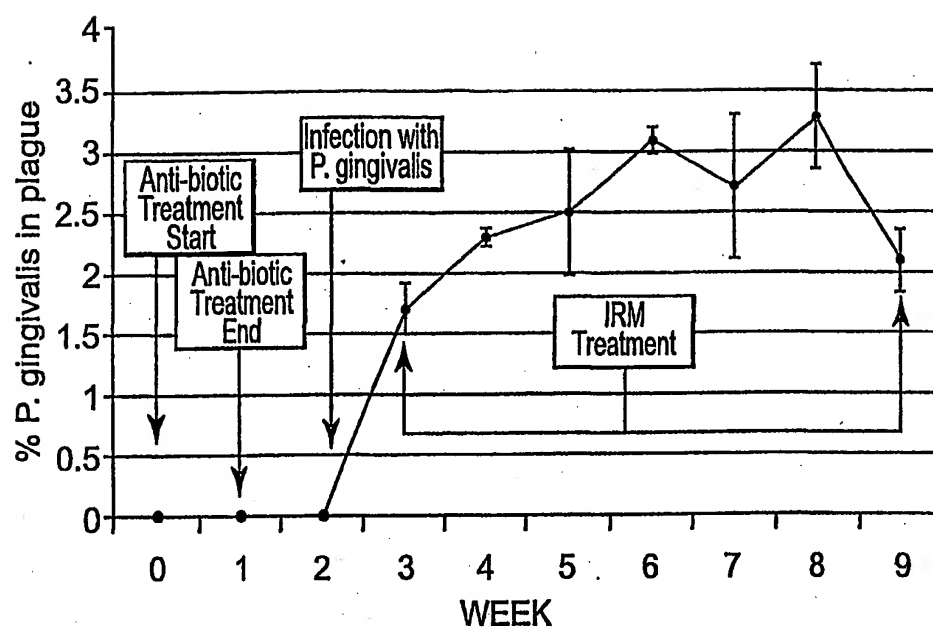
25. The use according to claim 19 wherein the periodontal tissue is the patient's periodontal pocket.
- 5 26. The use according to claim 19 wherein the periodontal tissue is the patient's gingiva.
27. The use according to claim 19 wherein the periodontal disease is chronic adult periodontitis.
- 10 28. The use according to claim 19 wherein the pharmaceutical formulation is in the form of a gel.
- 15 29. The use according to claim 19 wherein the pharmaceutical formulation is in the form of a transmucosal patch.

1/4



**Fig. 1**

2/4

**Fig. 2**

3/4

Effect of IRM on Bone Loss in *P. gingivalis* Infected Mice  
1 mg/kg Dosage Level

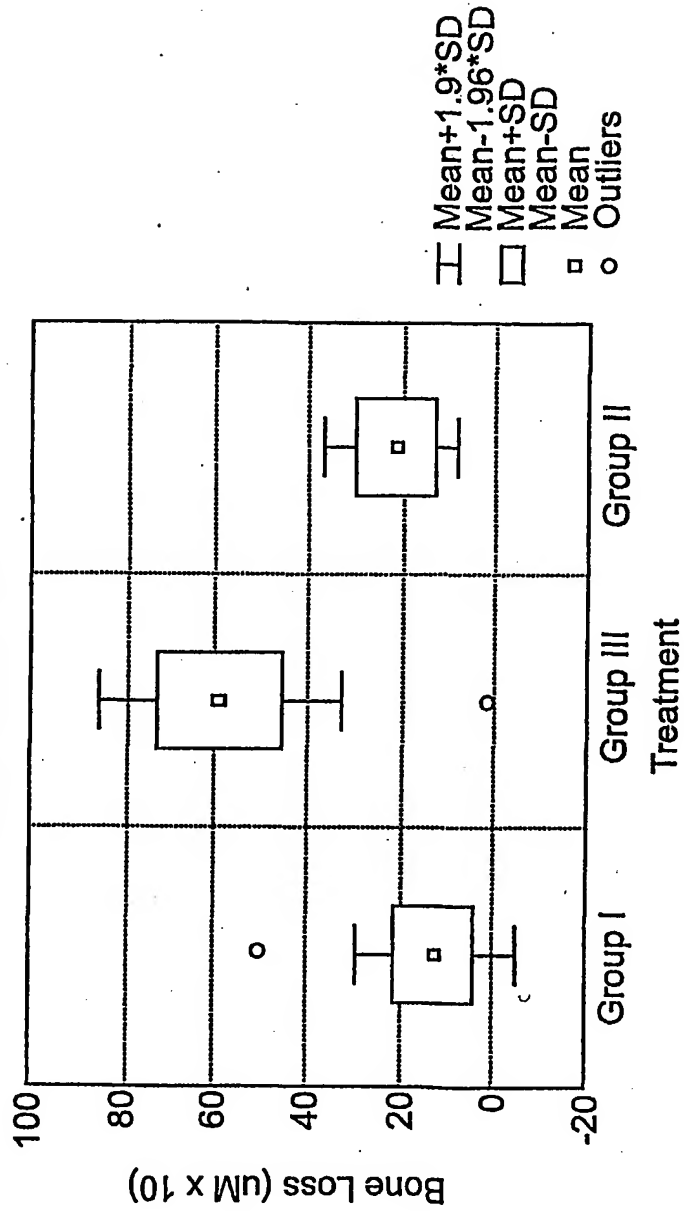
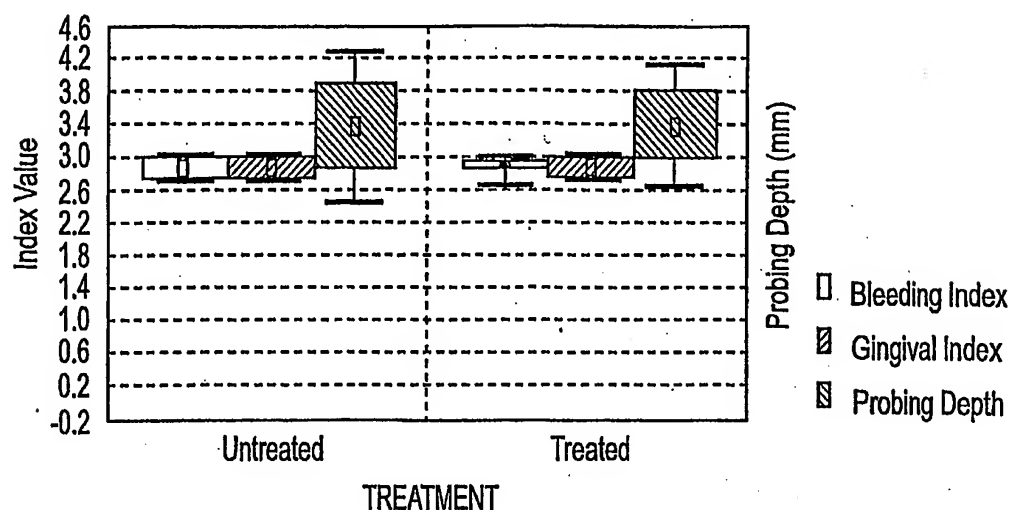


Fig. 3

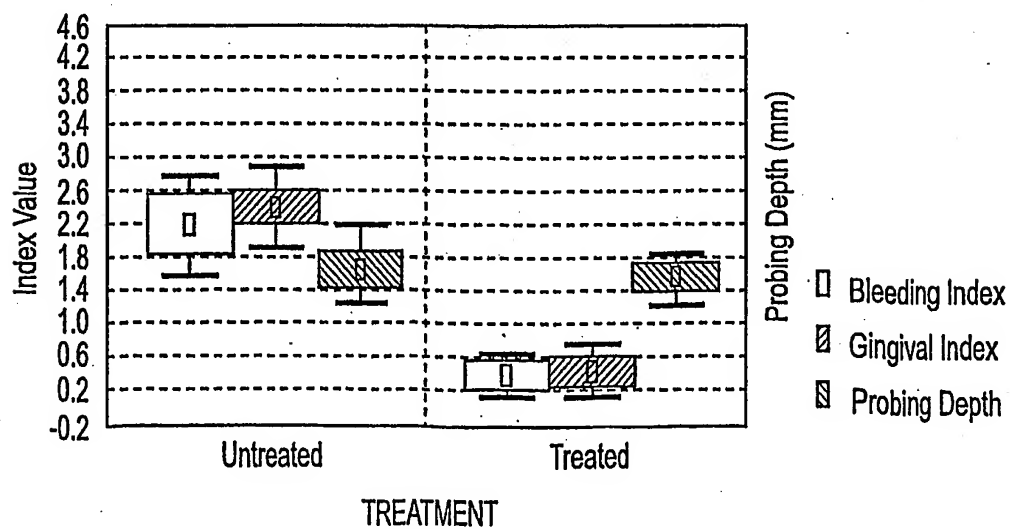


4/4

Clinical Measures - Baseline  
Mean; Box: Mean-SE, Mean+SE; Whisker: Mean-1.96\*SE, Mean+1.96\*SE (n=42 sites)

**Fig. 4a**

Clinical Measures - Baseline  
Mean; Box: Mean-SE, Mean+SE; Whisker: Mean-1.96\*SE, Mean+1.96\*SE (n=42 sites)

**Fig. 4b**

## INTERNATIONAL SEARCH REPORT

Inte I Application No

PCT/US 02/18944

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/429 A61K31/47 A61K31/435

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, FSTA, CHEM-ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 76518 A (3M INNOVATIVE PROPERTIES CO) 21 December 2000 (2000-12-21) cited in the application page 20, line 6	1-3, 5-23, 25-29
P,X	WO 02 07725 A (ALTEON INC) 31 January 2002 (2002-01-31)  page 16, line 16-36	1,2, 5-22, 25-29
X	US 5 854 257 A (ARMITAGE BERNARD JOHN ET AL) 29 December 1998 (1998-12-29) column 6, line 35-42 column 6, line 53-55  -/-	1,5-21, 25-29

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

6 November 2002

Date of mailing of the international search report

20/11/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Skjöldebrand, C

## INTERNATIONAL SEARCH REPORT

Inte      d Application No  
PCT/US 02/18944

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KORNMAN KENNETH S: "Host modulation as a therapeutic strategy in the treatment of periodontal disease." CLINICAL INFECTIOUS DISEASES, vol. 28, no. 3, March 1999 (1999-03), pages 520-526, XP009000169 ISSN: 1058-4838 abstract	1,5-21, 25-29

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1, 5-21, 25-29

Present independent claims 1 and 19 relate to the use of a compound defined by reference to a desirable characteristic or property, namely an "immune response modifier". Claims 20 and 21 use a similar functional definition.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, namely those parts relating to the compounds in claims 2-4.

It follows that the above objection is valid for depending claims 5-18, and 25-29, as they rely on the same definition of the compound.

Due to said unclear definition, the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that only a small fraction of these documents can be cited in the search report.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 02/18944

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☒ Claims Nos.: 1, 5-21, 25-29  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Inter Application No  
PCT/US 02/18944

Patent document cited in search report		Publication date	Patent family member(s)	Publication date			
WO 0076518	A	21-12-2000	AU 5328100 A	02-01-2001			
			AU 5328400 A	02-01-2001			
			AU 6334900 A	02-01-2001			
			BR 0011433 A	05-03-2002			
			CN 1353609 T	12-06-2002			
			CN 1354663 T	19-06-2002			
			CN 1355701 T	26-06-2002			
			CZ 20014363 A3	13-03-2002			
			CZ 20014364 A3	13-03-2002			
			EP 1198232 A1	24-04-2002			
			EP 1198233 A1	24-04-2002			
			EP 1187613 A1	20-03-2002			
			HU 0201431 A2	28-08-2002			
			HU 0201664 A2	28-08-2002			
			NO 20015502 A	07-02-2002			
			NO 20015503 A	08-02-2002			
			NO 20015504 A	07-02-2002			
			SK 17922001 A3	04-04-2002			
			SK 17932001 A3	04-06-2002			
			SK 17972001 A3	04-06-2002			
			TR 200103575 T2	21-06-2002			
			TR 200103576 T2	21-06-2002			
			WO 0076518 A1	21-12-2000			
			WO 0076505 A1	21-12-2000			
			WO 0076519 A1	21-12-2000			
			US 6331539 B1	18-12-2001			
			US 6451810 B1	17-09-2002			
			WO 0207725	A	31-01-2002	AU 8054601 A	05-02-2002
						AU 8055101 A	05-02-2002
						WO 0208210 A1	31-01-2002
WO 0207725 A1	31-01-2002						
US 2002103182 A1	01-08-2002						
US 2002068729 A1	06-06-2002						
US 5854257	A	29-12-1998	AU 3652895 A	02-05-1996			
			DE 69524114 D1	03-01-2002			
			DE 69524114 T2	18-07-2002			
			EP 0784622 A1	23-07-1997			
			JP 10506906 T	07-07-1998			
			WO 9611199 A1	18-04-1996			